

Captopril: evaluation of low doses, twice-daily doses and the addition of diuretic for the treatment of mild to moderate hypertension

VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP* ON ANTIHYPERTENSIVE AGENTS

From the Cooperative Studies Program of the Veterans Administration Medical Research Service

Summary

1. We randomized 475 men whose diastolic blood pressure was 92-109 mmHg to either placebo- or captopril-treated (37.5, 75 and 150 mg/day) groups for 7 weeks.

2. After 7 weeks, the placebo-treated patients were given hydrochlorothiazide (25 mg twice daily), as were two-thirds of each captopril-treated group, and they were observed for 7 additional weeks.

3. Captopril reduced blood pressure by $12.2 \pm 0.8/9.4 \pm 0.4$ mmHg at 7 weeks ($n = 323$) and captopril plus placebo by $10.3 \pm 1.9/10.2 \pm 0.9$ at 14 weeks ($n = 83$); placebo by $2.0 \pm 1.7/3.4 \pm 0.8$ ($n = 76$); captopril plus hydrochlorothiazide by $24.4 \pm 1.1/16.2 \pm 0.6$ ($n = 173$). The effect of low-dose captopril was similar to that of a high dose. The effect of twice-daily captopril appeared to be equal to that of

thrice-daily treatment but monitoring studies are needed to confirm this.

4. Only 15 out of 384 (3.9%) of patients were dropped from the study because of adverse effects.

5. Low-dose captopril may be useful in patients with mild to moderate hypertension.

Key words: captopril, hydrochlorothiazide.

Introduction

Captopril (SQ 14 225), an oral angiotensin converting enzyme inhibitor, was proposed as an ideal antihypertensive drug because it was targeted to a major humoral system responsible for sustaining elevated arterial pressure [1]. Indeed, captopril was effective in lowering arterial pressure even in patients who had low plasma renin activity and it was not associated with the adverse effects of the sympatholytic drugs [2]. Unfortunately, captopril had adverse effects, including a rash, neutropenia and proteinuria. Its initial use, however, had been restricted to severely ill patients and patients with severe hypertension resistant to multiple drug combinations. In general, very high doses (450 mg or more) of captopril were used [3]. We designed this study on patients with mild, uncomplicated hypertension to determine whether captopril was effective as a hypotensive agent in doses much lower than had been used previously and to determine if lower effective doses were associated with fewer adverse effects. We also sought to determine the degree of hypotension induced by the addition of hydrochlorothiazide to captopril and to determine whether captopril could be administered twice rather than three times daily.

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Methods

We enrolled 722 ambulatory male veterans whose diastolic (Korotkoff phase V) blood pressure was 92–109 mmHg and who met other qualifying criteria. All patients gave fully informed, written consent before they were enrolled. The protocol had been approved by a central human studies committee and similar committees at each of the seven participating centres. Patients were withdrawn from current medication for at least 2 weeks and then given a placebo capsule. Patients meeting the blood pressure entry criteria and compliance requirements (checked by count of pills remaining in a special blister pack) were randomized to taking a capsule which was identical in appearance with the placebo capsule but contained one of the following: placebo, captopril 12.5 mg, 25 mg, 37.5 mg or 50 mg. All of these medications were to be taken three times a day with the exception of captopril 37.5 mg, which was taken twice daily. The blind was preserved by placing a placebo as the mid-day dose on the blister pack. After 7 weeks (phase A), all patients were given a tablet that contained either hydrochlorothiazide (25 mg) or placebo and were instructed to take it twice daily. All patients previously given placebo instead of active captopril were given active hydrochlorothiazide so that no patients remained in the study on placebo alone beyond this point. All other patients receiving active captopril were randomized such that one-third of each dose group received placebo and two-thirds received active hydrochlorothiazide. The patients were followed for an additional 7 weeks (phase B), at

which time they were either returned to placebo for 2 weeks or entered into a long-term trial of captopril. Appropriate tests of leucocytes, blood chemistry and urine protein excretion were made.

Results

Of the 722 men enrolled, 475 (65.8%) qualified for randomization; 399 completed phase A and 315 finished phase B. The data which follow have been derived from these patients. The racial distribution was 248 (52.2%) white, 222 (46.7%) black and 5 (1.1%) other. Their average age was 55.0 years and 58.4% of them had previously received treatment for hypertension.

The blood pressure results are presented in Table 1. During phase A, all doses of captopril were equally effective in reducing blood pressure. The twice-daily performed as well as the thrice-daily dose and the percentage at goal (diastolic blood pressure less than 91 mmHg) was the same. During phase B, the 83 patients who were randomized to have placebo instead of active hydrochlorothiazide added to captopril maintained approximately the same level of blood pressure as in phase A, except for an increase of systolic pressure in patients taking 12.5 mg thrice daily and a slight additional blood pressure reduction in patients taking 37.5 mg twice daily and 50 mg thrice daily. The 173 remaining captopril-treated patients who received hydrochlorothiazide experienced a marked further reduction in both systolic and diastolic blood pressure. There was no difference in the response

TABLE 1. Blood pressure reduction achieved by captopril and captopril plus hydrochlorothiazide

Mean blood pressures are reported in mmHg \pm SE. Base, baseline; SBP, systolic blood pressure; DBP, diastolic blood pressure; Goal, goal blood pressure (<91 mmHg diastolic); HCTZ, hydrochlorothiazide; *n* = number in group. Captopril doses are recorded by mg given thrice daily (except 37.5 mg, which was given twice daily).

	Placebo	Phase A				Phase B									
		Captopril				Captopril plus placebo				Captopril plus hydrochlorothiazide					
		12.5 mg	25 mg	37.5 mg	50 mg	12.5 mg	25 mg	37.5 mg	50 mg	HCTZ	12.5 mg	25 mg	37.5 mg	50 mg	
<i>n</i>	76	79	78	85	81	23	20	22	18	59	44	41	39	48	
Base SBP	146.0	147.6	147.6	149.3	147.4	149.4	148.9	149.9	145.0	145.6	146.1	148.1	148.8	146.8	
	±1.6	±1.7	±1.3	±1.5	±1.8	±3.1	±2.8	±3.6	±3.1	±1.8	±2.4	±1.7	±1.9	±2.3	
−Δ SBP	2.0	9.9	11.6	13.7	13.3	3.1	11.6	13.1	14.7	11.6	23.3	26.5	25.8	22.5	
	±1.7	±1.7	±1.6	±1.7	±1.5	±2.4	±3.7	±3.9	±4.9	±1.7	±2.6	±2.2	±2.6	±1.8	
Base DBP	97.8	97.0	98.1	97.5	97.9	97.7	98.6	97.4	96.8	97.6	96.2	98.2	97.5	98.4	
	±0.5	±0.4	±0.5	±0.5	±0.5	±0.9	±0.8	±0.9	±1.2	±0.6	±0.6	±0.7	±0.7	±0.7	
−Δ DBP	3.4	8.6	9.2	9.5	10.3	8.3	8.2	12.6	11.9	8.2	16.6	15.5	14.5	17.6	
	±0.8	±0.9	±0.9	±0.9	±0.8	±1.7	±1.7	±2.1	±2.0	±1.0	±1.1	±1.2	±1.2	±1.1	
% at goal	36.8	65.8	58.9	63.5	70.3	56.5	47.3	76.1	83.3	55.9	95.5	85.3	82.1	89.5	

of the two groups which received 75 mg of captopril per day.

During phase A, white patients tended to respond to captopril better than black patients. Black patients responded better when hydrochlorothiazide was added to placebo during phase B and the racial differences were abolished in the captopril-treated groups by the addition of the diuretic.

During phase A, 2.6% of patients taking placebo and 3.1% taking captopril developed a rash. During phase B, 1.7% of the patients receiving the placebo plus hydrochlorothiazide, 3.6% of those receiving captopril plus placebo and 1.2% of those receiving captopril plus hydrochlorothiazide had a rash. The overall incidence of the development of a rash in the captopril-treated patients was 15 out of 384 (3.9%), of which five patients were receiving the 150 mg/day dose. Therefore the incidence in the low dose group was 2.4%.

Eighteen patients were withdrawn from the trial owing to drug intolerance. These were evenly distributed across all of the groups. Two patients taking captopril 37.5 twice daily and 50 mg thrice daily were withdrawn on account of urticaria; three taking diuretic plus captopril 12.5, 25 and 50 mg thrice daily had a maculopapular rash; two taking the diuretic plus 25 mg thrice-daily and 37.5 mg twice-daily captopril had loss of taste, which returned on discontinuation of the drugs; two taking the diuretic plus captopril 12.5 and 25 mg thrice daily had nausea and vomiting. Proteinuria occurred in three patients. Urinary protein excretion rose in one patient taking captopril 12.5 mg thrice daily from a baseline value of 126 mg to 665 mg after 5 weeks of captopril treatment and returned to baseline after captopril had been discontinued. In another patient urinary protein excretion rose from a baseline level of over 453 mg/day to 1600 mg/day after 12 weeks of captopril 50 mg thrice daily. One patient who was randomized to placebo treatment excreted 800 mg/day and 1200 mg/day of protein 4 days later. He returned to normal within 1 month without intervention. Three patients were withdrawn owing to intolerable hypotension; two were taking 50 mg of captopril thrice daily and one the diuretic and 25 mg of captopril thrice daily. One patient taking 37.5 mg of captopril twice daily complained of intolerable headaches. Two patients taking placebo were withdrawing owing to drug intolerance. One complained of weakness, dizziness and dry mouth after the first dose and refused to

return. One complained of headache, impotence, dysuria and urinary frequency after 5 weeks of therapy.

Discussion

Captopril 50 mg thrice daily was included in this experimental design because it was then considered to be the lowest effective dose. This study demonstrates clearly that captopril alone in lower doses (37.5 and 75 mg daily) reduces blood pressure in mildly hypertensive patients as well as captopril 150 mg daily. The expected enhancing effect of added diuretic was also clear. We believe that our data suggest that captopril can be administered twice rather than thrice daily, but definitive proof requires blood pressure monitoring experiments. Previous unpublished data have suggested that captopril would not be effective alone in black patients, but our study shows a good effect. Racial response was equalized by the addition of a diuretic. Withdrawals for adverse effects were very low and in the range we have experienced in previous studies of diuretics and β -adrenoceptor-blocking agents. That is not to imply that effects such as rashes did not occur, but that discontinuation of the drug was usually unnecessary. It was also very difficult to be certain whether a rash was due to captopril or to the diuretic or to the combination.

We believe that this short-term study demonstrates that the use of captopril in low doses may be extendable to the general population of hypertensive patients and might no longer need to be restricted to severe or resistant hypertensive patients.

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